REMARKS

I. Status of the Claims

Claims 1-55 are pending in the application. Claims 1-55 stand rejected. Independent claims 1, 18, 19, 20 and 54 have been amended above to define the subject matter of those claims more clearly and to make those claims more user-friendly. This amendment does not change the scope or content of claims 1, 18, 19, 20 and 54.

Claims 38 and 39 have been rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicants appreciate the Examiner's indication that claims 38 and 39 are allowable.

New claims 56-59 have been presented above. Support for new claims 56-59 may be found throughout the specification and figures as originally filed. Support for new claim 56 may be found, for example, at page 7, lines 2-3, original claim 1, and at Figure 1. Support for new claim 57 may be found, for example, at original claim 1 and at page 20, lines 1-11. Support for new claim 58 may be found, for example, at original claim 1, Figure 1 and page 12, line 20. Support for new claim 59 may be found, for example, at original claim 1, at page 20, first paragraph, page 23, second full paragraph and at Fig. 14.

Applicants respectfully request reconsideration of the application.

II. Information Disclosure Statements

Applicants filed an Information Disclosure Statement on June 5, 2002 and also filed Supplemental Information Disclosure Statements on October 2, 2002 and August 5, 2003. Nothing in the Office Action indicates whether or not the Examiner has considered the citations listed in these IDS's.

Applicants respectfully request that the Examiner consider the citations listed in these statements.

III. Amendments to the Specification

In the amendments above, a blank line has been inserted between the paragraph beginning on page 4, line 20, and the paragraph beginning on page 5, line 3. Also in the amendments above, in the "Brief Description of the Drawings," each of the paragraphs has been indented. Also in the amendments above, a blank line has been inserted between the paragraph beginning on page 13, line 19, and the paragraph beginning on page 14, line 22.

The Examiner asserts that it is improper to incorporate essential material by reference that is a foreign application or patent or a publication. While this may be a correct statement of the incorporation by reference guidelines, the publications incorporated by reference on pages 3, 4, 5 and 6 are listed in the background section, and M.P.E.P. 608.01(p) provides that it is proper and allowed to incorporate non-patent publications by reference if they are background material.

As a precautionary matter and without any determination of whether or not Li et al. contains essential or non-essential matter, Applicants have included the text of the "Coil Construction" section of the Experimental Section of Li et al. in the specification. The "incorporation by reference" language has been removed from page 24. A Declaration executed by Dr. Timothy L. Peck is enclosed herewith stating that the text added to the application is the same as the text incorporated by reference. Therefore, this amendment overcomes the objection.

M.P.E.P. 608.01(p) provides that it is proper to incorporate a pending and commonly owned patent application by reference, as so done by Applicants on page 26. The Examiner is permitted to request a copy of said application. See M.P.E.P. 608.01(p)(I)(A)(1). If the Examiner requests a copy of the application, then Applicants will provide such a copy along with a declaration stating the copy consists of the same material incorporated by reference. Further, Applicants have amended the paragraph on page 26 to recite PCT/US01/31333 filed on October 5, 2001 and published as WO0228532. The PCT application claims priority to U.S. Application Serial No. 60/239,010. Applicants have also amended this paragraph to recite U.S. Application No.

10/033,315 (Pub. No. 2002/0176804), which is a continuation of the listed PCT Application.

With respect to the use of the terms "for example," "such as," and "or the like" in the specification, the Examiner asserts that such terms raise the issue of indefiniteness under 112, second paragraph. Applicants disagree with the Examiner.

The plain language of 35 U.S.C. § 112, second paragraph, indicates that this statute is only relevant to clarity of the claims and not the terms used in the specification. That is, because 112, second paragraph, expressly refers to the language of the claims, this paragraph cannot be used to object to any portion of the specification. Further, Applicants are allowed to use the terms "for example," "such as," and "or the like" to describe various exemplary embodiments within the scope of the invention. Accordingly, the objection is improper and should be withdrawn.

IV. Claims 1-37 and 40-55 are Patentable over Freeman

Claims 1-37 and 40-55 are rejected under § 103(a) over Freeman (US 6,194,900). Applicants traverse the rejection.

The claims of the present invention are directed to an NMR probe, and systems including the NMR probe, comprising multiple NMR detection sites, wherein each NMR detection site comprises a sample holding void and an associated NMR microcoil and wherein each NMR microcoil is operative to detect one or more analytes in the sample holding void with which the NMR microcoil is associated. Claims 1-53 and new claims 56-59 also include a controllable fluid router operative to direct fluid sample to the multiple NMR detection sites. Thus, using the present invention, multiple and independent samples in different sample voids can be simultaneously and independently detected using NMR. For example, the specification states on page 20 that

> The multiple NMR sites are provided to allow for increased functionality and/or throughput. With multiple NMR sites the user is able to perform multiple NMR tests simultaneously which increases the rate in which results may be obtained. Furthermore the NMR detection sites may be optimized for different types of testing allowing a single probe to be used for a number of tests.

These advantages cannot be achieved using the methods and devices of Freeman. Instead, the device of Freeman only includes a single detection compartment. See Abstract and Figures. Therefore, the Freeman device does not enable multiple and independent samples to be independently routed to specific, independent sample voids.

The Examiner asserts that Freeman teaches a moveable manifold that allows a fluid to enter the Freeman device at selected aperture positions and direct fluid samples into a separation compartment that is serially connected to a microcoil. The Examiner also asserts that each aperture is a site or point in fluid communication with a microcoil from which detection of a signal from a sample to be analyzed can be obtained and that such disclosure renders the present claims obvious. Applicants disagree with the Examiner and traverse the rejection.

The Freeman device contains a single detection compartment in fluid communication with a separation compartment to enable the detection of separated analytes. See Col. 28, lines 50-56. It is difficult to conceive practically that precisely spaced analytes (e.g. those resulting from a chromatographic separation) could align with the exact geometrical placement of multiple NMR coils of a single, series-configured Freeman manifold in such a way to enable simultaneous detection from the multiple analytes. The limitations of the Freeman device prevent realization of the benefits of the present invention. For example, in Freeman, routing and detection of analytes is not independent.

In addition, all analytes in Freeman are part of the same fluidic stream and therefore dissolved in the same solvent. An action carried out on one analyte, e.g., the length of time required for NMR acquisition, would necessarily affect the actions carried out on all other analytes in Freeman due to the series connection and single fluidic stream of Freeman. In stark contrast, the current invention provides devices and methods for independently routing independent samples to specific detection voids, including voids that are optimized for a specific NMR function. For example, detection of a specific nuclear species, or detection where the detection void has been optimized to a specific solvent or sample class, or detection where the detection void is volumetrically sized to optimize detection sensitivity for a specific concentration of sample, or detection where

the detection void is optimized for multi-dimensional NMR acquisition. Thus, the Freeman invention is designed (and stated by Freeman, e.g. col. 33, lines 50-55) for prolonged acquisition by replication of coils in a series configuration along a single fluidic path for the purposes of increased data acquisition time and therefore increased signal-to-noise, and Freeman does not teach or suggest independent routing of independent samples to one or more of a multiplicity of independent detection voids, including the use of intelligence for optimization and/or decision-making for routing from one independent detection void to another independent detection void. For example, decision-making could be based upon data collected from detection void #1, whereby the sample could be routed to detection void #7 for further analysis. The series configuration of Freeman requires samples to pass sequentially from coil #1 to coil #2, and furthermore requires that ALL analytes in the stream progress in an identical manner. In summary, the manifold of Freeman allows for entry of fluid from different apertures of the manifold into the single NMR detection compartment, but multiple, NMR detection voids, as that term is used in the present claims, is not found in the disclosure of Freeman.

Further, Freeman is admitted by the Examiner to be serially connected to a microcoil (see page 7, number 10, of the Office Action). Thus, Freeman discloses a single microcoil in serial connection to apertures of a manifold. The only disclosure of multiple microcoils in Freeman is at Col. 33, lines 50-55. However, even in this cryptic description, seemingly perhaps referring to locations spaced along a capillary, the connection is still serial. At any point in time, the device of Freeman only contains a single detection site, *i.e.* a given manifold aperture aligned with the single detection compartment. Moreover, Freeman can't do, nor is it an obvious extension of Freeman because of the very nature of the subject matter at hand, to carry out multiple and independent NMR experiments simultaneously due to isolation concerns within a given device. The present invention achieves this result, and certain embodiments of the invention achieve this result on the capillary scale.

With reference to independent claims 1, 18, 19 and 20, Freeman fails to teach or suggest any NMR probe, or system including an NMR probe, comprising multiple NMR detection sites each comprising a sample holding void and an associated NMR microcoil, wherein each NMR microcoil is operative to detect one or more analytes in the sample holding void in which the NMR microcoil is associated; and a controllable fluid router operative to direct fluid sample to the multiple NMR detection sites. Instead, as discussed above, Freeman only teaches a device having a single detection compartment configured in a fluidically series manner. Thus, claims 1, 18, 19 and 20 are patentable over Freeman.

Each of claims 2-17 and 32-34 depends directly or indirectly from claim 1 and is patentable over Freeman for at least the same reasons as claim 1 and for the additional element(s) recited therein.

Each of claims 21-31, 35-37, and 40-53 depends directly or indirectly from claim 20 and is patentable over Freeman for at least the same reasons as claim 20 and for the additional element(s) recited therein.

With particular reference to claim 25, because Freeman fails to teach or suggest the multiple NMR detection sites of the present invention, the device of Freeman cannot include multiple NMR detection sites each optimized for different nuclear species. Therefore, claim 25 is patentable over Freeman.

With particular reference to claim 27, Freeman fails to teach or suggest two-dimensional NMR studies. Instead, Freeman only teaches that his single, series topology rf microcoil device can be used to display and store multinuclear NMR spectra and that NMR can be used to obtain two- and three-dimensional structure. That is, Freeman teaches that its rf microcoil could be used to detect different nuclei (e.g., ^{1}H, ^{13}C, etc.) and can be used for determining the two and/or three-dimensional structures of analytes. This teaching, however, is insufficient to render claim 27 obvious. To render claim 27 obvious, the Examiner is required to provide objective evidence that demonstrates that the person of ordinary skill in the art would immediately envisage two-dimensional NMR studies in view of Freeman. No such evidence has been provided by the Examiner, and, therefore, claim 27 is patentable over Freeman.

With particular reference to claim 28, because Freeman fails to teach or suggest the multiple NMR detection sites of the present invention, the device of Freeman cannot include multiple NMR detection sites that are optimized for different sample sizes. Thus, claim 28 is patentable over Freeman.

With particular reference to claim 29, because Freeman fails to teach or suggest the multiple NMR detection sites of the present invention, the device of Freeman cannot include multiple NMR detection sites that are optimized using different materials. Thus, claim 29 is patentable over Freeman.

With particular reference to claim 30, Freeman fails to teach or suggest that the detection sites can be made of fused silica and PEEK. With particular reference to claim 31, Freeman fails to teach or suggest that the detection sites can be made of fused silica and polytetrafluoroethylene. The Examiner asserts that even though Freeman does not disclose the use of PEEK or polytetrafluoroethylene, Freeman's disclosure of transparent materials would render claims 30 and 31 obvious. Applicants disagree with the Examiner.

To render claims 30 and 31 obvious, the Examiner bears the burden of providing objective evidence that establishes that the person of ordinary skill in the art, in view of Freeman, would be motivated to use fused silica and PEEK or fused silica and polytetrafluoroethylene. No such objective evidence has been provided. Therefore, each of claims 30 and 31 is patentable over Freeman.

With particular reference to claim 32, because Freeman fails to teach or suggest the multiple NMR detection sites of the present invention, the device of Freeman cannot include multiple NMR detection sites that are optimized differently. Thus, claim 32 is patentable over Freeman.

With particular reference to claim 40, the Examiner asserts that outlet port 630 is an operative component in communication with the fluid pathway. Applicants disagree with the Examiner and traverse the rejection.

The outlet port of Figs 26A and 26B (outlet port 630) is not an operative component as that term is used in the present claims. The specification states at page 32, first paragraph, that

> The operative component can be any number of devices that interact with the fluid in the module including, for example, sensors, sample preparation devices, pumps, heaters, coolers, ultrasonic devices and even additional NMR sites. The operative component may also be any number of devices that do not interact with the fluid. Examples, for instance, include microprocessors, micro-controllers and memory module.

Thus outlet port 630, which only allows exiting of fluid from the Freeman device, is not an operative component in communication with the fluid pathway. Accordingly, claim 40 is patentable over Freeman.

With particular reference to claim 41, the Examiner asserts that Freeman's disclosure of laser ablation renders claim 41 obvious. Applicants disagree with the Examiner and traverse the rejection.

The laser ablation disclosed in Freeman is an external device used to construct the substrate of Freeman's device and is not a heating device in communication with the fluid pathway as recited in claim 41. Therefore, claim 41 is patentable over Freeman.

With particular reference to claim 42, the Examiner asserts that the rotor is capable of rotating about the stator, and the rotation produces a sound therefore. Applicants disagree with the Examiner and traverse the rejection.

The rotor disclosed in Freeman is for operation of the manifold. See Col. 29, lines 41-46. That is, the rotor is for movement of the manifold and is not a sonication device. Accordingly, claim 42 is patentable over Freeman.

With particular reference to claim 47, the Examiner asserts that Freeman suggests that an "operative component is a photodiode array" because use of the laser ablation process photo-dissociates the chemical bonds, and therefore Freeman knows and determines the amount of light incident on the sample. Applicants disagree with the Examiner and traverse the rejection.

It is well established that a photodiode array is an electronic device that detects light. Disclosure of a physical process by Freeman does not provide sufficient teaching or suggestion to render an electronic device obvious. Accordingly, claim 47 is patentable over Freeman.

With particular reference to claim 50, the Examiner asserts that the central computer of Freeman has memory and this teaching renders claim 50 obvious. Applicants disagree with the Examiner and traverse the rejection.

The central computer of Freeman does not have a memory module in communication with the fluid pathway. As mentioned above, the use of intelligence for optimization and/or decision-making for routing a specific sample from one independent detection void to another independent detection void is unique to the present invention. In contrast, the central computer of Freeman, as admitted by the Examiner, simply controls data acquisition, signal storage and signal processing, which are basic computational actions generally associated with data acquisition. Thus, claim 50 is patentable over Freeman.

With reference to independent claim 54, Freeman fails to teach or suggest an NMR probe module comprising at least one fluid inlet port, operative to receive a fluid sample; a fluid pathway comprising multiple fluidic channels in fluid communication with the at least one fluid inlet port, for the transport of fluid sample to be tested; and multiple NMR detection cells, each in fluid communication with a corresponding one of the multiple channels and comprising: an enlarged void for holding a fluid sample, and an associated NMR microcoil, wherein each NMR microcoil is operative to detect one or more analytes in the enlarged void in which the NMR microcoil is associated. As discussed above, the device of Freeman only includes a single detection compartment surrounded by an rf microcoil. Thus, claim 54 is patentable over Freeman.

Claim 55 depends from claim 54 and is patentable over Freeman for at least the same reasons as claim 54 and for the additional element(s) recited therein.

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V. Conclusion

In view of the foregoing amendments and remarks, claims 1-55 and new claims 56-59 are in condition for immediate allowance.

Respectfully submitted,
Peck et al.

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Dated

Peter D. McDermott (Reg. No. 29,411)
Attorney for Applicants
Banner & Witcoff, LTD.
28 State St. - 28th Floor
Boston, MA 02109
617.720.9600